

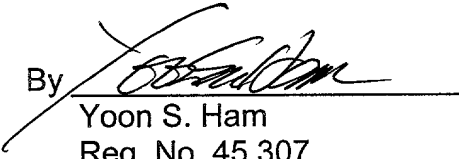
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED / ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		ATTORNEY'S DOCKET NUMBER P67297US0
		US APPLICATION NO. (If known, see 37 CFR 1.5) 09/926590
INTERNATIONAL APPLICATION NO. PCT/KR/01151	INTERNATIONAL FILING DATE 16 October 2000	PRIORITY DATE CLAIMED 24 March 2000
TITLE OF INVENTION A SOMATOTROPIN COMPOSITION WITH IMPROVED SYRINGEABILITY		
APPLICANT(S) FOR DO/EO/US Nam Joong KIM and Je Phil RYOO		

Applicant herein submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information.

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☐ A proper Demand for Internatl. Preliminary Examination was made by the 19th month from earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
 - a. ☒ is transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☒ has been transmitted by the International Bureau.
 - c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
 - a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
 - b. ☐ have been transmitted by the International Bureau.
 - c. ☐ have not been made; however, the time limit for making such amendments has NOT expired.
 - d. ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☒ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the Internatl. Preliminary Examination report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☒ An assignment document for recording. A separate cover sheet compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A **FIRST** preliminary amendment.
☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☒ Other items or information:
 - International Search Report (Austria)
 - PCT Request Form
 - PCT/IB/301 Form
 - PCT/IB/304 Form
 - PCT/IB/306 Form
 - PCT/IB/308 Form
 - First Page of Publication

US APPLICATION NO. (If known, see 37 CFR 1.5) 09/926590		INTERNATIONAL APPLICATION NO. PCT/KR00/01151		ATTORNEY'S DOCKET NUMBER P67297US0	
17. <input checked="" type="checkbox"/> The following fees are submitted: Basic National Fee (37 CFR 1.492(a)(1)-(5)): Internatl. prelim. examination fee paid to USPTO (37 CFR 1.492 (a) (1)) .. \$710.00 No international preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (2)) but international search fee paid to USPTO (37 CFR 1.445(a)(2)) .. \$740.00 Neither international preliminary examination fee (37 CFR 1.492 (a) (3)) nor international search fee (37 CFR 1.445(a)(2)) paid to USPTO) \$1040.00 International preliminary examination fee paid to USPTO (37 CFR 1.492 (a) (4)) and all claims satisfied provisions of PCT Article 33(2)-(4) \$100.00 Search Report prepared by the EPO or JPO (37 CFR 1.492 (a) (5)) \$890.00 <div style="text-align: right;">ENTER APPROPRIATE BASIC FEE AMOUNT =</div>				CALCULATIONS	PTO USE ONLY
				\$ 1040.00	
Surcharge of \$130.00 for furnishing the oath or declaration later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(e)).				\$	
Claims	Number Filed	Number Extra	Rate		
Total Claims	14 - 20 =	-0-	x \$18.00	\$	
Independent Claims	1 - 3 =	-0-	x \$84.00	\$	
Multiple Dependent Claim(s) (if applicable)			+ \$280.00	\$	
TOTAL OF ABOVE CALCULATIONS =				\$ 1040.00	
Reduction by 1/2 for filing by small entity , if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).				\$	
SUBTOTAL =				\$ 1040.00	
Processing fee of \$130 for furnishing the English translation later than <input type="checkbox"/> 20 <input type="checkbox"/> 30 months from the earliest claimed priority date (37 CFR 1.492(f))				\$	
TOTAL NATIONAL FEE =				\$ 1040.00	
Fee of \$40.00 for recording the enclosed assignment (37 CFR 1.21(h)). Assignment must be accompanied by appropriate cover sheet (37 CFR 3.28, 3.31).				\$ 40.00	
TOTAL FEES ENCLOSED =				\$ 1080.00	
				Amt. to be refunded:	\$
				Amt. charged:	\$
a. <input checked="" type="checkbox"/> A check in the amount of \$ <u>1080.00</u> to cover the above fees is enclosed. b. <input type="checkbox"/> Please charge my Deposit Account No. <u>06-1358</u> in the amount of \$ _____ to cover the above fees. A duplicate copy of this sheet is enclosed. c. <input checked="" type="checkbox"/> The Commissioner is hereby authorized to charge my account any additional fees set forth in §1.492 during the pendency of this application, or credit any overpayment to Deposit Account No. <u>06-1358</u> . A duplicate copy of this sheet is enclosed.					
SEND ALL CORRESPONDENCE TO: <div style="display: flex; justify-content: space-between;"> <div style="width: 45%;"> JACOBSON HOLMAN PLLC 400 7th Street, N.W., Suite 600 Washington, DC 20004 202-638-6666 CUSTOMER NUMBER: 00136 </div> <div style="width: 45%; text-align: right;"> By  Yoon S. Ham Reg. No. 45,307 </div> </div>					

09/926590

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants: KIM et al.

Serial No.: New

Filing Date: November 21, 2001

For: A SOMATOTROPIN COMPOSITION WITH IMPROVED
SYRINGEABILITYPRELIMINARY AMENDMENTAssistant Commissioner of Patents
Washington, D.C. 20231

Sir:

Prior to initial examination, please amend the above-identified application as follows:

IN THE SPECIFICATION

On page 1, immediately following the title, please insert the following sentence:

--This is a nationalization of PCT/KR00/01151 filed October 16, 2000 and published in English.--

REMARKS

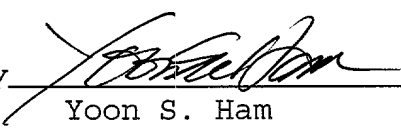
The foregoing Preliminary Amendment is requested in order to place the application in better form for examination.

Early action on the merits is respectfully requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By


Yoon S. Ham

Reg. No. 45,307

400 Seventh Street, N.W.
Washington, D.C. 20004-2201

(202) 638-6666

Atty. Docket: P67297US0

Date: November 21, 2001

YSH:crj

A SOMATOTROPIN COMPOSITION WITH IMPROVED SYRINGEABILITY

5 FIELD OF THE INVENTION

The present invention relates to a composition containing somatotropin having activity in vivo, and particularly, to a composition which can obtain the sustained release effect of the pharmaceutical to avoid the inconvenience of daily administration as well as have the suitable syringeability for being parenterally
10 administered into animals to solve problems during injection, in which somatotropin is mixed with excipients.

DESCRIPTION OF THE PRIOR ART

15 Recently, somatotropin which can be produced in a large scale by using recombinant DNA technology according to development of genetic engineering has been commercially available for increasing the productivity of milk in cattle, and has been studied for improving feed efficiency and meat quality in swine.

Most of formulations developed hitherto for administering somatotropin
20 having activity in vivo are simply the long acting types wherein a large amount of somatotropin is administered to avoid the inconvenience of daily administration.

For example, USP No. 5411951 and No. 5474980 disclose sustained release formulations prepared by adding a gelling agent such as aluminum monostearate into vegetable oil; by gelling the oil by heating; and by mixing somatotropin or other drugs with it homogeneously, because drugs become phase-separated and precipitated in short time when only vegetable oil is used. These techniques have been already used to prepare the sustained release formulations of various drugs such as known antibiotics(USP No. 2491537, No. 2507193 and No. 3016330), pamoate salts of oxazepines(USP No. 3676557) or relaxin which is a kind of hormone(USP No. 2964448), adrenocorticotrophic hormone(USP No. 3869549), luteinizing hormone releasing factor(USP No. 4256737), gonadotropin(USP No. 3852422) and insulin(USP No. 2143590, No. 2174862, No. 2882203, No. 2920014 and No. 3102077) and the like.

There are similar prior art techniques using oil simply for preparing sustained release formulations. For example, EP 211691 discloses that somatotropin is mixed with a mixture of wax and oil and EP 213851 discloses that the sustained release formulation is prepared by mixing somatotropin with a mixture of oil and commercially available glyceride release-modifying agent. Also, EP 314421 discloses that sustained release formulations of somatotropin are prepared by adding absorption-controlling material(e.g., calcium stearate and dextran) to oil. But these are also the formulations wherein the active ingredients in the known injectable formulations containing oil used for other drugs have been substituted with somatotropin.

In addition, the sustained release techniques without using oil have been attempted. For example, in EP 193917, somatotropin was mixed with water-

soluble carbohydrate polymer(e.g., starch, dextrin) to improve the sustained release effect. However, it has shorter duration of action than formulations mixed in oil, and it may do harm on stability of somatotropin due to its water-solubility.

Different techniques from the above-mentioned techniques have been attempted for lengthening duration of action of somatotropin formulations. USP No. 4861580 discloses that the sustained release formulation of somatotropin was prepared as a liposome type by using lipid-soluble materials such as alpha-tocopherol hemisuccinate Tris salt, phosphatidyl choline and phosphatidyl ethanolamine. And in USP No. 4675189, the sustained release formulation of somatotropin was prepared as a microcapsule type by using biocompatible polymer. And in USP No. 4857506, the sustained release formulation of somatotropin was prepared as a multiple water-in oil-in water(W/O/W) emulsion type. But somatotropin formulations according to these techniques are inadequate to be commercialized since the formulations have short duration of action or very complicated manufacturing processes requiring high techniques, and low stability as well as low recovery rate of making somatotropin into a desired form.

By using quite different techniques, implantable formulations, which are solid dosage forms, were prepared for improving the sustained release of somatotropin. These techniques have been described in USP No. 4452775, No. 4761289, No. 4765980, No. 4774091, No. 4786501, No. 4863736, No. 5035891, No. 5198422, No. 5228697, No. 5356635, No. 5595752 and EP 246540 and 462959, and PCT/US92/01877, PCT/US91/08129, PCT/US90/01340, PCT/AU87/00139 and the like. These techniques tried to secure sustained

release of somatotropin by implanting somatotropin into the animal body by surgical operation using an expensive device, or implanting a compressed somatotropin form into the animal body using a special implant apparatus. These implanting techniques are preferred for obtaining a desirable release amount and
5 sustained effect of somatotropin. However, the implanting process is too difficult to be performed on animals and animals also feel very uncomfortable due to the foreign substance.

USP No. 5520927 and Korean Patent No. 177306 attempted to lengthen duration of action of somatotropin using tocopherol acetate which has been used
10 as an antioxidant to prevent oxidation reaction of drugs which may occur in a somatotropin composition simply containing oils as described above. However, since the viscosity of tocopherol acetate or vitamin A dramatically increases as the temperature decreases, the somatotropin composition shows such poor syringeability that cannot be used in winter or cold areas, or immediately after
15 being taken out of a refrigerator which is the storage condition of the somatotropin composition. Thus, it needs several tens of minutes to melt the composition under ambient temperature before use. Further, the syringeability under ambient temperature is not so good that it requires the great effort and long time for injection of the composition, resulting in doubling the pain of animal being
20 administered.

The inventors of the present invention have conducted intensive researches to solve the above-mentioned problems of conventional somatotropin formulations.

SUMMARY OF THE INVENTION

The present inventors have developed a somatotropin-containing composition which can be administered into the body by injection that is the most general administration method hitherto as well as which can be injected with superior syringeability, even in winter of dropping temperatures or immediately after being taken out of a refrigerator which is the storage condition of somatotropin composition, and which has the same or better sustained release effect and physiological activity of somatotropin as those of conventional somatotropin formulations. The composition of the present invention consists of somatotropin, at least one of lipid-soluble vitamins and at least one of pharmaceutically acceptable lubricants.

An object of the present invention is to provide a composition comprising somatotropin and vitamins with improved syringeability, which can be more easily administered into body by injection that is the most general administration method hitherto, which can decrease injection frequency resulting in reducing the labor and cost for administration as well as animals' pain, and which can increase the reproduction efficiency and the productivity of milk according to administration of somatotropin, while decrease the incidence of mastitis and metabolic diseases, by administering somatotropin with vitamins simultaneously, not separately.

Another object of the present invention is to provide a composition comprising somatotropin, which can be used in cold areas or in winter as well as immediately after being taken out of a refrigerator that is the storage condition of somatotropin composition, and which can be administered without difficulty due to of its improved syringeability under room temperature.

In accordance with the present invention, there is provided a composition consisting of somatotropin, at least one of lipid-soluble vitamins and at least one of pharmaceutically acceptable lubricants. The present invention has many advantages, including providing a composition containing somatotropin with improved syringeability. These and other features, aspects, and advantages of the present invention will become better understood with reference to the following description and appended claims.

DETAILED DESCRIPTION

10 The present invention provides a composition consisting of somatotropin, at least one of lipid-soluble vitamins and at least one of pharmaceutically acceptable lubricants. The present invention will hereinafter be described in more detail. The vitamins to be mixed with somatotropin in the present composition are lipid-soluble vitamins, such as vitamin A or vitamin E, which are preferred drugs in preparing a mixed formulation since they can make protein 15 drugs such as somatotropin stable by delaying the drugs from binding with water.

In addition to the above-described advantage of the formulation, vitamin A increases the sense of vision, particularly dark adaptation in relation with rhodopsin and iodopsin, the visual dyes in rods and cones which sensitize light in the retina. It also improves abnormal dryness, degeneration, keratinization and 20 ulceration of mucus, xerophthalmia and keratomalacia and increases the resistance against various diseases. In addition, it has been reported to be an essential element for maintenance of epithelial tissue and the growth of bone and teeth and to have a growth-stimulating activity.

Vitamin E deficiency in animals causes the white muscle disease which partly changes the color of muscle fiber into gray and makes the muscles atrophied. Initial symptoms of muscular atrophy is that the entire body loses its flexibility and appears to be stiff, and gradually becomes weak and paralyzed, and then difficulty in breathing occurs. As the disease progresses, animals having severe symptoms become unable of lactation. Also, vitamin E is referred as an anti-sterility vitamin because it overcomes the sterility of animals, and it stimulates growth of animals. In addition, vitamin E helps normal reproduction processes, prevents the abnormal development of muscle and may prevent cerebromalacia, irregular activity of muscle, muscle spasm, ataxia and tonic spasm.

Hitherto, somatotropin compositions have been developed considering only the productivity and reduction of administration frequency for target animals. For example, somatotropin compositions have been designed for dairy cow, focusing on increase of the productivity of milk and reduction of the dairy farmer's labor according to the frequent administration by lengthening the in vivo duration of action of somatotropin. However, if somatotropin compositions have been administered into animals, focusing only on productivity, without considering the health conditions of animals, it may often cause side effects. The incidence of diseases such as mastitis which is a major disease of dairy cow occurs mainly due to environmental factors and hygienic factors when milking, however, it has been also reported that the incidence frequency of mastitis depends on the ability of each dairy cow. That is, it is known that mastitis more often occurs in more milk-productive cows than less milk-productive cows. Therefore, when somatotropin is used to increase the milk productivity, proper treatment according to each cow's

0996550 112101

milk productivity, as well as clean milking condition, is necessary to prevent the incidence of mastitis. There are many factors to cause the mastitis as mentioned above. Thus, it is preferred to increase dairy cows' resistance against bacteria as a countermeasure for prevention of mastitis. To this end, proper farm cares
5 would be important. However, such prevention effect can be obtained by providing appropriate drugs, for example, vitamins. That is, when vitamin A or vitamin E is deficient, the mucous epithelial cells of teat canal, teat cistern and the like become keratinized, which induces the infection and proliferation of bacteria. The proliferated bacteria invade the gland cistern, resulting in severe mastitis. In
10 addition, they lower the synthesis of immunoglobulin and keratin which are protecting materials in interior teat canal, thereby causing serious mastitis.

There are several methods for examining the mastitis, but the general method is to count the number of somatic cells in milk. The criterion for diagnosis is the number of somatic cells per 1 ml of milk, which determines level of mastitis.
15 The lower the number, the better the milk, then the milk is recognized as having been produced from a dairy cow without mastitis.

Therefore, the present invention has prepared compositions containing somatotropin, which increase the productivity of milk, enhance the health of target animals by minimizing side effects which might be caused by the increase of milk
20 productivity, and maximize convenience of the dairy farmer who administers the compositions into animals by improving the syringeability markedly without affecting the physiological activity of the protein drug, somatotropin.

Among the lipid-soluble vitamins, particularly vitamin A may cause side effects when administered in a large amount. Thus, the formulations should be

prepared with extra care. The effects of the somatotropin and the vitamins can be maximized when an appropriate amount of the vitamins is added to the composition.

In the composition of the present invention, the pharmaceutically acceptable lubricant may be one which can be mixed with the lipid-soluble vitamins and the lubricant may be used alone or in a mixture of at least two lubricants.

The lubricants for improving syringeability of the composition which are the core of the present invention are pharmaceutically acceptable materials which do not affect the physiological activity of somatotropin. In the composition of the present invention, the pharmaceutically acceptable lubricants may include pharmaceutically acceptable alcohol or its derivatives, preferably benzyl alcohol, ethyl alcohol, isopropyl alcohol, butyl alcohol, or the like. In the composition of the present invention, the pharmaceutically acceptable lubricants also include esters of fatty acid and alcohol, such as ethyl oleate, isopropyl myristate, isopropyl laurate, isopropyl lanolate, isopropyl palmitate, or the like; unsaturated fatty acids, for example, liquid unsaturated fatty acids, such as oleic acid, linoleic acid, linolenic acid, or the like; esters of acid and aromatic alcohol, such as benzyl benzoate or the like; and other materials which can be mixed with the lipid-soluble vitamins such as polyoxyethylene alkyl ether (bridges), tetrahydrofurfuryl alcohol polyethylene glycol ether sold under the trademark GLYCOFUFOL™ (c.f. "Handbook of Pharmaceutical Excipients"), derivatives of polyethylene glycol, glycerin, or the like. It is preferable that the pharmaceutically acceptable lubricant in the present invention is one which can be mixed with the lipid-soluble vitamins.

The lubricants in the present invention include pharmaceutically acceptable materials which can be well mixed with lipid-soluble vitamins, particularly vitamin A or vitamin E or derivatives thereof, to improve the syringeability. Such lubricant may be used alone or in a mixture of at least two lubricants.

5 Somatotropin which can be used in the composition of the present invention may be generally the somatotropin of various animals, but bovine somatotropin or porcine somatotropin is preferred. Also, in the composition of the present invention, natural somatotropin purified highly from the pituitary gland of animals or somatotropin produced artificially by recombinant DNA technology can
10 be used.

In the composition of the present invention, the lipid-soluble vitamin may be vitamin A or its derivative, or vitamin E or its derivative. In the composition of the present invention, vitamin A or its derivative, which does not affect the physiological activity of somatotropin, for examples, any type of optical isomer of
15 vitamin A, vitamin A acetate, vitamin A palmitate, vitamin A propionate, etc., can be used. Also, vitamin E or its derivative, which does not affect the physiological activity of somatotropin, for examples, any type of optical isomer of vitamin E, vitamin E acetate, vitamin E succinate, vitamin E nicotinate, vitamin E phosphate, etc., can be used in the composition of the present invention.

20 In the composition of the present invention, the somatotropin is preferably present in an amount of from 10 to 50 % by weight based on the total weight of the composition. In the composition of the present invention, vitamin A or its derivative is preferably present in an amount of from 100,000 to 5,000,000 vitamin A units and more preferably from 300,000 to 3,500,000 vitamin A units per 1 g of

somatotropin. In the composition of the present invention, vitamin E or its derivative is preferably present in an amount of from 500 to 12,000 vitamin E units and more preferably from 1,500 to 8,500 vitamin E units per 1 g of somatotropin. In the composition of the present invention, the lubricant may be preferably
5 present in an amount of from 0.5 to 25 % by weight and more preferably from 1 to 15 % by weight, based on the total weight of the composition.

In preparing the composition of the present invention, somatotropin in a powder form may be prepared by lyophilizing a somatotropin solution alone, or by lyophilizing fine particles prepared by adding a pharmaceutical excipient(e.g.,
10 lecithin, etc.) to a somatotropin solution, or by lyophilizing the mixture of a somatotropin solution with a stabilizing agent such as sucrose, mannitol, trehalose and the like. When the lyophilized somatotropin powder is used, water content and particle size should be considered. It is preferable that the water content is 3% or below for the stability of somatotropin. The particle size which is related to
15 phase-separation after long storage and syringeability of the composition, is preferably 10 μm or below. When the particle size of the lyophilized somatotropin is bigger than the desired size, it will be necessary to carry out ball mill or air jet mill process in order to reduce the particle size, without changing the quality of the somatotropin. For example, the mixed composition of somatotropin and vitamins
20 may be prepared by homogeneously mixing the somatotropin powder with an appropriate amount of lipid-soluble vitamins. Then, the composition of the present invention may be prepared by homogeneously mixing the mixture with an appropriate amount of pharmaceutically acceptable lubricants. Alternatively, the composition of the present invention may be prepared by homogeneously mixing

the somatotrin with lipid-soluble vitamins and pharmaceutically acceptable lubricants. It will be apparent to those skilled in the art that the composition of present invention may be formulated into any appropriate dosage form, and may be administered in any appropriate manner.

5 The previously described versions of the present invention have many advantages, including providing somatotropin-containing injectable compositions with improved syringeability under the ambient temperature and cold temperature which maximize the convenience in administering somatotropin into animals' body by injection; and providing somatotropin-containing injectable compositions which
10 can increase the reproduction efficiency and the milk productivity, while prevent the incidence of mastitis and metabolic diseases in cow and the like according to the increase of milk productivity, by administering somatotropin with lipid-soluble vitamins, particularly vitamin A, vitamin E or the like simultaneously.

 The present invention will now be described in more detail in connection
15 with the following examples, which should be considered as being exemplary only and not limiting the present invention.

EXAMPLE 1

20 3000 ml of bovine somatotropin(LG Chemical Ltd. Biotech Research Institute) solution(130.5 mg/ml) was divided into three lyophilization trays by 1000 ml respectively and lyophilized in a freeze-dryer for about 48 hours. The lyophilized powder was ground using an air-jet mill to make particles of average 8 μ m size of diameter. Thus obtained bovine somatotropin in a powder form had

1.4 % of water content, which was measured in a heating-type moisture analyzer.

Then the lyophilized bovine somatotropin powder was homogenously mixed with vitamin E acetate(1g = 1,000 unit, ROCHE) and benzyl alcohol in a homogenizer, according to the amount described below in Table 1.

5 2 g of each homogenously mixed composition was taken to fill in a polypropylene syringe of 9.8 mm size of diameter having a 16-gauge needle of 1.7 cm size of length to prepare a sample for measuring syringeability. The prepared samples were stored under ambient temperature(22°C) and cold temperature(4°C) for 24 hours. The syringeability was measured by proceeding in a rate of 7.8 cm
10 per minute using a syringeability measuring device(Test Stand Model 2252 and CPU gauge 9500 series, Aikoh Engineering, Japan) at each temperature. The measured results were shown in Table 1.

Table 1

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of benzyl alcohol (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.70	0.30	4.65	10.72
	14.25	0.75	2.86	10.01
	14.00	1.00	2.51	9.37
	13.75	1.25	2.13	7.73
	13.50	1.50	1.87	5.82
2.00	18.00	0	3.42	11.95
	16.75	1.25	1.82	5.66
8.00	12.00	0	9.04	>20
	10.75	1.25	3.23	9.99
* bST : abbreviation of bovine somatotropin				

EXAMPLE 2

- 5 Following the procedure as described in Example 1 except that isopropyl alcohol was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 2.

Table 2

Amount of *bST(g)	Amount of vitamin E acetate (g)	Amount of isopropyl alcohol (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.50	0.50	2.78	9.74
	14.00	1.00	1.83	4.67
	13.50	1.50	1.65	2.90
* bST : abbreviation of bovine somatotropin				

EXAMPLE 3

- 5 Following the procedure as described in Example 1 except that ethyl alcohol was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 3.

Table 3

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of ethyl alcohol (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.50	0.50	4.39	14.29
	14.00	1.00	2.94	12.84
	13.50	1.50	2.00	8.71
* bST : abbreviation of bovine somatotropin				

EXAMPLE 4

Following the procedure as described in Example 1 except that ethyl oleate was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 4.

5

Table 4

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of ethyl oleate (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.00	1.00	2.33	9.48
	13.75	1.25	2.47	7.99
	13.50	1.50	2.15	5.51
	13.00	2.00	1.70	4.07
	12.00	3.00	1.58	2.12
* bST : abbreviation of bovine somatotropin				

EXAMPLE 5

10 Following the procedure as described in Example 1 except that benzyl benzoate was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 5.

Table 5

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of benzyl benzoate (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.00	1.00	2.83	10.48
	13.00	2.00	2.06	7.55
	12.75	2.25	2.04	7.11
	12.50	2.50	1.98	4.79
	12.00	3.00	1.82	3.98
* bST : abbreviation of bovine somatotropin				

EXAMPLE 6

- 5 Following the procedure as described in Example 1 except that Bridge 30 was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 6.

Table 6

Amount of *bST(g)	Amount of vitamin E acetate (g)	Amount of Bridge 30 (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	12.00	3.00	1.93	4.24
* bST : abbreviation of bovine somatotropin				

EXAMPLE 7

Following the procedure as described in Example 1 except that oleic acid was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 7.

5

Table 7

Amount of *bST(g)	Amount of vitamin E acetate (g)	Amount of oleic acid (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	12.00	3.00	1.72	4.20
* bST : abbreviation of bovine somatotropin				

EXAMPLE 8

Following the procedure as described in Example 1 except that GLYCOFUROL™ was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 8.

15

Table 8

Amount of *bST (g)	Amount of vitamin E acetate(g)	Amount of GLYCOFUROL™ (g)	Syringeability(kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.00	1.00	3.10	9.95
	13.75	1.25	2.63	9.56
	13.50	1.50	2.28	8.61
	13.25	1.75	2.05	7.56
	13.00	2.00	2.06	5.61
	12.00	3.00	1.72	3.32
* bST : abbreviation of bovine somatotropin				

EXAMPLE 9

- 5 Following the procedure as described in Example 1 except that polyethylene glycol 400 dimethylether was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 9.

Table 9

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of polyethylene glycol 400 dimethylether (g)	Syringeability (kgf)	
			Ambient temp.	Cold temp.
5.00	15.00	0	5.24	14.76
	14.25	0.75	3.15	11.29
	13.50	1.50	2.48	6.58
	12.00	3.00	1.62	2.97
* bST : abbreviation of bovine somatotropin				

EXAMPLE 10

- 5 Following the procedure as described in Example 1 except that benzyl alcohol was used as lubricant and a mixture of vitamin E acetate and vitamin A acetate (1g = 2,800,000 IU, Sigma, U.S.A.) was used as vitamin, the composition was prepared and the syringeability was measured. The results were shown in Table 10.

Table 10

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate (g)	Amount of benzyl alcohol (g)	Syringeability (kgf)	
				Ambient temp.	Cold temp.
5.00	13.20	1.80	0	5.19	14.82
	12.60	0.90	1.50	2.16	5.61
	12.20	1.80	1.00	2.16	8.82
	11.70	1.80	1.50	2.04	5.59
	10.70	1.80	2.50	1.92	2.89
	8.35	5.40	1.25	2.06	5.64
* bST : abbreviation of bovine somatotropin					

EXAMPLE 11

- 5 Following the procedure as described in Example 10 except that benzyl benzoate was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 11.

Table 11

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate (g)	Amount of benzyl benzoate (g)	Syringeability (kgf)	
				Ambient temp.	Cold temp.
5.00	13.20	1.80	0	5.19	14.82
	11.20	1.80	2.00	2.52	9.56
	10.70	1.80	2.50	2.20	6.63
	10.20	1.80	3.00	1.83	6.29
* bST : abbreviation of bovine somatotropin					

EXAMPLE 12

Following the procedure as described in Example 10 except that a mixture of benzyl alcohol and benzyl benzoate was used as lubricant, the composition was prepared and the syringeability was measured. The results were shown in Table 12.

Table 12

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate (g)	Amount of benzyl alcohol (g)	Amount of benzyl benzoate (g)	Syringeability (kgf)	
					Ambient temp.	Cold temp.
5.00	13.20	1.80	0	0	5.19	14.82
	11.70	1.80	1.00	0.50	2.16	6.96
	11.20	1.80	1.00	1.00	1.63	6.71
	13.00	0	1.00	1.00	1.61	5.16
	10.70	1.80	1.00	1.50	1.67	4.67
	10.20	1.80	1.00	2.00	1.53	3.43
* bST : abbreviation of bovine somatotropin						

EXAMPLE 13

Following the procedure as described in Example 10 except that ethyl oleate was used as lubricant and vitamin A palmitate(1g = 1,700,000 IU, ROCHE, Switzerland) instead of vitamin A acetate was used, the composition was prepared and the syringeability was measured. The results were shown in Table 13.

Table 13

Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A palmitate (g)	Amount of ethyl oleate (g)	Syringeability (kgf)	
				Ambient temp.	Cold temp.
5.00	12.00	3.00	0	3.56	13.86
	10.00	5.00	0	3.27	12.22
	11.00	3.00	1.00	2.01	6.23
	10.00	3.00	2.00	1.62	2.82
* bST : abbreviation of bovine somatotropin					

EXAMPLE 14

5 100 ml of bovine somatotropin (LG Chemical Ltd. Biotech Research Institute) solution (130.5 mg/ml) was mixed with 26.1 g of lecithin by using a homogenizer for 30 minutes. Then, the mixture was ground in a microfluidizer to make particles of 200 nm or below size of diameter. The suspension was filtrated through a filter of 0.22 μm pore size for sterilization, transferred into one

10 lyophilization tray and lyophilized in a freeze-dryer for about 48 hours. The lyophilized powder was ground using an air-jet mill to make particles of average 8 μm size of diameter. Thus obtained bovine somatotropin in a powder form had 1.6 % of water content, which is measured in a heating-type moisture analyzer.

Using the lyophilized lecithin-bovine somatotropin powder, the composition

15 was prepared and the syringeability was measured according to the procedure as described in Example 1 except that each amount was used as described below in Table 14. The results were shown in Table 14.

Table 14

Amount of *bST(g))	Amount of lecithin (g)	Amount of vitamin E acetate (g)	Amount of benzyl alcohol (g)	Syringeability (kgf)	
				Ambient temp.	Cold temp.
5.00	1.00	14.00	0	4.97	15.25
	1.00	12.75	1.25	2.83	10.12
* bST : abbreviation of bovine somatotropin					

EXAMPLE 15

5 Animal tests were carried out using the compositions prepared as described below in Table 15. Female SD rats(180~220 g) of 8-9 weeks old were used. The interval between light and darkness in a room was 12 hours, and water and feed were freely accessible. 8 rats per one composition were used and 4 rats were included in a cage for an experiment. The rats were weighed before

10 administration of the compositions. Then, the rats were randomly separated into the treated groups, based on the average body weight and the standard error. The body weight before administration of the composition was considered as a standard body weight of each rat. 80 mg of each composition(corresponding to 20 mg of bovine somatotropin) was subcutaneously injected into the abdominal

15 region of each rat. Then, the rats were weighed at regular time everyday for 9 consecutive days. As a control group, 8 rats without any injection were weighed during the above test period by the same method. The cumulative mean weight gain of rats of each group was indicated in Table 16, which was measured after administration of the composition.

Table 15

Composition No.	Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate (g)	Type and amount (g) of lubricant
1	5.00	15.00	0	0
2		13.20	1.80	0
3		13.50	0	Benzyl alcohol 1.50
4		11.70	1.80	Benzyl alcohol 1.50
5		12.20	1.80	Benzyl alcohol 1.00
6		14.00	0	Ethyl oleate 1.00
* bST : abbreviation of bovine somatotropin				

Table 16

		Composition No.						
		1	2	3	4	5	6	Negative control
Day	1	8.03	12.79	13.23	11.48	12.25	13.03	5.11
	2	21.51	23.06	21.56	23.18	21.80	23.20	10.48
	3	23.73	24.58	25.63	28.03	24.89	23.94	12.43
	4	26.78	28.18	27.81	32.36	33.11	28.39	9.40
	5	29.55	33.31	34.18	37.00	36.55	35.10	15.53
	6	37.79	40.95	32.76	41.46	41.59	39.20	19.93
	7	40.05	44.59	39.78	48.24	45.01	44.70	21.36
	8	35.49	40.84	38.38	44.49	44.38	40.61	19.74
	9	35.09	42.53	43.18	49.70	44.79	42.76	22.88
* Negative control : control that received no composition.								
* Unit : g								

EXAMPLE 16

- 5 Following the procedure as described in Example 15 except that compositions were prepared by mixing two kinds of lubricants as described below in Table 17, animal tests were carried out. The cumulative mean weight gain of rats of each group was indicated in Table 18, which was measured after administration of the composition.

Table 17

Composition No.	Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of vitamin A acetate(g)	Type and amount (g) of lubricant
1	5.00	13.20	1.80	0
2		11.20	1.80	Benzyl alcohol 1.00, Benzyl benzoate 1.00
* bST : abbreviation of bovine somatotropin				

Table 18

		Composition No.		
		1	2	Negative control
Day	1	10.63	10.86	1.71
	2	19.95	18.89	7.14
	3	24.08	23.45	7.45
	4	28.10	27.73	9.51
	5	32.26	33.20	13.55
	6	38.18	39.63	17.46
	7	42.44	43.09	15.64
	8	45.33	46.24	15.84
	9	43.75	44.81	19.96
* Negative control : control that received no composition.				
* Unit : g				

EXAMPLE 17

Following the procedure as described in Example 15 except that compositions were prepared as described below in Table 19 with the lecithin-bovine somatotropin prepared as described in Example 14 and genetically derived 5 dwarf female rats(90-120 g) of 8 weeks old instead of normal rats were used, animal tests were carried out. The cumulative mean weight gain of rats of each group was indicated in Table 20, which was measured after administration of the composition.

10 Table 19

Composition No.	Amount of *bST (g)	Amount of vitamin E acetate (g)	Amount of lecithin (g)	Type and amount (g) of lubricant
1	5.00	15.00	0	0
2		12.75	1.00	Benzyl alcohol 1.25
3		12.00	1.00	Benzyl alcohol 1.00, Benzyl benzoate 1.00
4		14.00	1.00	0
* bST : abbreviation of bovine somatotropin				

Table 20

		Composition No.				
		1	2	3	4	Negative control
Day	1	8.39	14.01	6.80	9.85	1.93
	2	12.49	17.59	13.48	11.57	3.45
	3	16.45	20.47	17.44	16.67	5.17
	4	20.25	27.63	23.58	22.87	7.37
	5	23.03	32.31	28.16	28.41	5.65
	6	28.87	35.99	31.14	31.71	8.29
	7	28.57	36.63	38.16	34.17	10.15
	8	26.21	36.19	40.56	33.55	11.61
	9	29.55	39.77	44.34	37.19	11.13
* Negative control : control that received no composition.						
* Unit : g						

As shown above in the Tables 16, 18 and 20, it was confirmed that the body weight of the treated group with the composition of the present invention according to the Examples 15-17, increased more than about 20 g than that of the negative control group at the 9th day after administration of the composition, the composition of the present invention had a biological effect equivalent or more to that of the composition without any lubricant, and the composition of the present invention had improved syringeability that might maximize the convenience of the diary farmer who administers the composition into animals.

Although the present invention has been described in detail with reference to the above specific embodiments, other embodiments are possible. Therefore, it should be apparent to those skilled in the art that various modifications and

•

20

[illegible]

What is claimed is:

1. A composition consisting of somatotropin, at least one of lipid-soluble vitamins, and at least one of pharmaceutically acceptable lubricants.

5

2. The composition according to Claim 1, wherein said somatotropin is somatotropin produced by recombinant DNA technology.

3. The composition according to Claim 1, wherein said somatotropin is present in
10 an amount of from 10 to 50 % by weight based on the total weight of the composition.

4. The composition according to Claim 1, wherein said lipid-soluble vitamin is vitamin A or its derivative, or vitamin E or its derivative.

15

5. The composition according to Claim 4, wherein said vitamin A or its derivative is present in an amount of from 100,000 to 5,000,000 vitamin A units per 1 g of somatotropin.

20 6. The composition according to Claim 4, wherein said vitamin E or its derivative is present in an amount of from 500 to 12,000 vitamin E units per 1 g of somatotropin.

7. The composition according to Claim 1, wherein said pharmaceutically acceptable lubricant is one which can be mixed with said lipid-soluble vitamins and

09026590-1-12104

said lubricant is used alone or in a mixture of at least two lubricants.

8. The composition according to Claim 7, wherein said pharmaceutically acceptable lubricant is alcohol or its derivative; ester of fatty acid and alcohol; 5 unsaturated fatty acid; ester of acid and aromatic alcohol; or other material which can be mixed with said lipid-soluble vitamins.

9. The composition according to Claim 8, wherein said alcohol or its derivative is benzyl alcohol, ethyl alcohol, isopropyl alcohol, butyl alcohol or the like.

10

10. The composition according to Claim 8, wherein said ester of fatty acid and alcohol is ethyl oleate, isopropyl myristate, isopropyl laurate, isopropyl lanolate, isopropyl palmitate or the like.

15 11. The composition according to Claim 8, wherein said unsaturated fatty acid is oleic acid, linoleic acid, linolenic acid or the like.

12. The composition according to Claim 8, wherein said ester of acid and aromatic alcohol is benzyl benzoate or the like.

20

13. The composition according to Claim 8, wherein said other material is polyoxyethylene alkyl ether, GLYCOFUROL, derivative of polyethylene glycol, glycerin or the like.

14. The composition according to Claim 7, wherein said lubricant is present in an amount of from 0.5 to 25 % by weight based on the total weight of the composition.

09:46:50.464
TUE 06 SEP 97

DECLARATION AND POWER OF ATTORNEY U.S.A.

ALL PATENTS, INCLUDING DESIGN
FOR APPLICATION BASED ON PCT; PARIS CONVENTION;
NON PRIORITY, OR PROVISIONAL APPLICATIONS

FOR ATTORNEYS' USE ONLY

ATTORNEYS' DOCKET NO.

P67297US0

As a below named inventor, I declare that my residence, post office address and citizenship are stated below next to my name, the information given herein is true, that I believe that I am the original first and sole inventor (if only one name is listed at 201 below), or an original, first and joint inventor (if plural inventors are named below at 201-203, or an additional sheet(s) attached hereto of the subject matter which is claimed and for which patent is sought on the invention entitled:

A SOMATOTROPIN COMPOSITION WITH IMPROVED SYRINGEABILITY

which is described and claimed in:

☐ the attached specification

☒ PCT International Application No. PCT/KR00/01151

filed October 16, 2000

☐ the specification in application Serial No. _____

filed _____

(if applicable) and amended on _____

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I hereby claim foreign priority benefits under Title 35, United States Code, §119 (a)-(d) of any foreign application(s) for patent as inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed:

Prior Foreign Application(s)

Priority Claimed

2000-0015091

KOREA

24 March 2000

☒

☐

(Number)

(Country)

(Day/Month/Year Filed)

Yes

No

(Number)

(Country)

(Day/Month/Year Filed)

☐

☐

(Number)

(Country)

(Day/Month/Year Filed)

☐

☐

I hereby claim the benefit under Title 35, United States Code, §119(e) of any United States provisional application(s) listed below:

Application No. _____

Filing Date _____

Application No. _____

Filing Date _____

I hereby claim the benefit under Title 35, United States Code, §120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of Title 35, United States Code, §112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application:

(Application Serial No.)

(Filing Date)

(Status: patented, pending, abandoned)

POWER OF ATTORNEY: As a named inventor, I hereby appoint the following attorneys (Registration No.) to prosecute this application, receive and act on instructions from my agent, and transact all business in the Patent and Trademark Office connected therewith. HARVEY B. JACOBSON, JR. (20,851); JOHN CLARKE HOLMAN (22,789); MARVIN R. STERN (20,849); ALLEN S. MELSER (27,215); MICHAEL R. SLOBASKY (20,421); JONATHAN L. SCHERER (20,851); IRWIN M. AISENBERG (19,007); WILLIAM E. PLAYER (31,400); YOON S. HAM (45,307) and NATHANIEL A. HUMPHRIES (22,772)

SEND CORRESPONDENCE TO: CUSTOMER NO. 00138

or

JACOBSON HOLMAN
PROFESSIONAL LIMITED LIABILITY COMPANY
400 SEVENTH STREET, N.W.
WASHINGTON, D.C. 20004

DIRECT TELEPHONE CALLS TO:

(please use Attorney's Docket No.) (202) 838-8888

JACOBSON HOLMAN
PROFESSIONAL LIMITED LIABILITY COMPANY

*Inventor(s) name must include at least one unabbreviated first or middle name.

201	FULL NAME OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE
202	FULL NAME OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE
203	FULL NAME OF INVENTOR	FAMILY NAME	GIVEN NAME	MIDDLE NAME
	RESIDENCE & CITIZENSHIP	CITY	STATE OR FOREIGN COUNTRY	COUNTRY OF CITIZENSHIP
	POST OFFICE ADDRESS	CITY	STATE OR COUNTRY	ZIP CODE

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

SIGNATURE OF INVENTOR 201*	SIGNATURE OF INVENTOR 202*	SIGNATURE OF INVENTOR 203*
DATE <u>Nov. 20, 2001</u>	DATE <u>Nov. 20, 2001</u>	DATE _____

☐ Additional inventors are named on separately numbered sheets attached hereto.

© JH 2001 (COPYING WITHOUT DELETIONS PERMITTED)